

	Standard Operating Procedure Adverse Events		SOP Number QS-102	Revision 4
			Effective Date 11/01/22	Page Page 1 of 7
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Title: QA Manager		Title: Quality Systems Manager		Title: VP of Quality & Regulatory Affairs

1.0 Purpose

The purpose of this procedure is to define the requirements for Adverse Event reporting. It is intended to ensure compliance to FDA Dietary Supplement and Nonprescription Drug Consumer Protection Act as it applies to 21 CFR 111 (Subpart O) and 21CFR Part 211 and establish and implement a system for reporting adverse incidents as a basis for effective identification and evaluation of adverse events, and timely submissions of Forms to the FDA and/or Canadian Authorities.

2.0 Scope

This procedure pertains to all dietary supplements (human and pet), or OTC products that are produced by Ion Labs, Inc. as a contract manufacturer on behalf of a customer. The customer is responsible for adverse event reporting unless a specific agreement has been signed by both parties, transferring responsibility to Ion Labs, Inc. Regarding reporting, Ion Labs will collaborate with the customer, when necessary.

3.0 Responsibility

- 3.1 It is the responsibility of Quality Management to implement, maintain and enforce this procedure. Quality Management is also responsible for determining if event reporting is warranted.
- 3.2 It is the responsibility of Production Management to assist with the investigation associated with any Adverse/Serious/Unexpected Adverse Event.

4.0 Definitions

- 4.1 **Dietary Supplement** – A product intended for ingestion that contains a dietary

ingredient intended to add further nutritional value to supplement the diet

- 4.2 **OTC** – Over-the-Counter Drug; drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and can be purchased by consumers without a prescription.
- 4.3 **Disability** – A substantial disruption of a person’s ability to conduct normal life functions.
- 4.4 **Initial Reporter** – The person who first notifies the responsible person about the serious adverse event and can be the injured person, a family member, or some other person (e.g., doctor, pharmacist).
- 4.5 **Life-Threatening Adverse Event** – Adverse events that place the person, in the view of the initial reporter at immediate risk of death from the serious adverse event as it occurred. Drug Related: **Life-threatening Adverse Drug Experience:** Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
- 4.6 **Non-serious** – Drug Related: Any Adverse Experience that is not fatal or life threatening that does not require inpatient hospitalization or prolonged hospitalization or is not permanently or severely disabling, or is not a congenital anomaly or does not jeopardize the patient/subject and/or is not an overdose.
- 4.7 **Responsible Person** – The manufacturer, packer, or distributor whose name appears on the label of a dietary supplement, or OTC marketed in the US and who is required to submit to FDA all serious adverse event reports associated with use of the dietary supplement in the US.
- 4.8 **Adverse Event** – Any health-related event associated with the use of a dietary supplement, or OTC that is adverse.
- 4.9 **Serious Adverse Event** – Results in death, a life-threatening experience, inpatient

hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly/birth defect or one that requires medical or surgical intervention to prevent such serious outcomes.

- 4.10 **Serious Adverse Drug Experience** – Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, this may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- 4.11 **Unexpected Adverse Event or Unexpected Suspected Adverse Reaction** – An adverse reaction, the nature or severity of which is not consistent with the applicable product information and is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. ***Drug Related:*** **Unexpected Adverse Drug Experience:** Any adverse drug experience that is not listed in the current approved labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling but differs from the event because of greater severity or specificity.

5.0 References

- 5.1 QS-101, SOP, Complaints
- 5.2 QS-101-F1, Form, Complaint Report Form
- 5.3 QS-112, SOP, Core Quality Systems and Quality Events
- 5.4 C-502, SOP, Record Storage, Retention, and Destruction
- 5.5 FDA SRP – Safety Reporting Portal

- 5.6 FDA Guidance for Industry, Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.

Information can be found at:

- 5.6.1 <http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm171383.htm>
- 5.7 Adverse Event Reporting Guidance, American Herbal Products Association (AHPA)
- 5.8 The US FDA CFSAN (Center for Food Safety and Applied Nutrition) -Adverse Event Reporting System supports information regarding adverse events and complaints for Dietary Supplement.
- 5.9 Health Canada Adverse Reaction Reporting System - MedEffect Canada/Canada Vigilance Program (Reference Guidance Document for Reporting Adverse Events for Marketed Products via the Marketed Health Products Directorate).
- 5.10 MedWatch –FDA Safety Information and Adverse Event Reporting Program for drug, device, food and cosmetics. MedWatch Form FDA 3500A is used by Facilities, Importers, Distributors and Manufacturers for Mandatory Reporting.

6.0 Procedure

- 6.1 Reference FDA’s Guidance for Industry “Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act” and AHPA’s “Adverse Event Reporting Guidance” for assistance in assessing adverse events for FDA reportability.
- 6.2 The VP of Quality and Regulatory Affairs or designee reviews the adverse event information obtained to verify that minimum information was documented and reflected in the Complaint Report, Form QS-101-F1 (for completing corresponding sections of FDA MedWatch Form 3500A).

- 6.3 Adverse Events are governed by the SOP QS-112 (Core Quality Systems and Quality Events) and may be documented and investigated under the Complaint Handling System. Complete all applicable sections of the FDA MedWatch Form 3500A electronically on the FDA.gov web site. Reference “FDA-3500A General Instruction (Excluding Device Sections).
- 6.4 If the required information is incomplete, at least three attempts to collect the information must be made and documented on the Complaint Report.
- 6.5 A decision must be made as to whether the event meets the definition of a Serious Adverse Event. A licensed physician may be contacted for consult to assess the seriousness.
- 6.6 Serious Adverse Events must be reported to FDA no later than 15 business days after the report is received by the responsible person.
- 6.6.1 Note per FDA: A report of each adverse drug experience that is both serious and unexpected must be made to FDA as soon as possible, but no later than 15 days after receiving information about the event. Persons required to file such 15-day Alert reports are also required to investigate and submit any new information to FDA.
- 6.7 A serious adverse event report must be submitted to FDA using one of the following electronic methods:
- Preferred: Electronic reporting, www.safetyreporting.hhs.gov, or
 - MedWatch Form 3500A Mandatory Reporting, <http://www.fda.gov/Safety/MedWatch/>.
- 6.7.1 A copy of the label on or within the retail packaging of the dietary supplement or OTC must be included with the serious adverse event report to FDA.

- 6.7.2 As part of the serious adverse event report, attach the following as appropriate: (1) hospital discharge summaries, (2) autopsy reports, (3) relevant laboratory data, and (4) other critical clinical data.
- 6.7.3 Any new medical information, related to a submitted serious adverse event report that is received within one year of the initial report shall be submitted to FDA no later than 15 business days after the new information is received by the responsible person.
- 6.8 For electronic submission, using the FDA SRP -Safety Reporting Portal, a confirmation email is sent to the responsible person containing a time stamped copy of their report upon its submission. This copy also contains an Individual Case Safety Report number to identify the report in any subsequent communications. The email is attached to the Complaint Report.
- 6.9 If a paper form is submitted (electronic is preferred), a serious adverse event report, along with a copy of the dietary supplement label and any other attachments must be mailed to FDA, Center for Food Safety and Applied Nutrition, Office of Food Defense, Communication and Emergency Response, CAERS Team, HFS-11, 5001 Campus Drive, College Park, MD 20740. A copy of the entire submission is attached to the Complaint Report.
- 6.10 Voluntary Adverse Event Reporting Contact Information is as follows:

For Special Nutritional Products (Dietary Supplements, Infant Formulas, Medical Foods), Cosmetics and Foods/Beverages –

E-mail: Consumer@fda.gov

E-mail: DSRSupport@fda.hhs.gov

Phone: 888-723-3366

7.0 Records

- 7.1 Complaint and Adverse Reporting documentation is maintained according to SOP

C-502 Record Storage, Retention and Destruction. Records will be scanned and retained, as appropriate.

8.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	01/23/14	New procedure.	14-0034	L. Derrick
1	09/01/16	Biennial review: Update to be in compliance with MedWatch guidelines.	16-0788	S. Millar
2	10/11/17	Reference assistance from production and operations for investigation associated with adverse events. Reference and list type of adverse events. Reference Health Canada Adverse Event Reporting System. Revise titles.	17-1258	S. Millar
3	04/22/20	Change to add reference to SOP QS-112. Remove reference to products where Ion Labs, Inc. appears on the label of the dietary supplement, cosmetic, OTC.	19-0604	S. Millar
4	08/05/22	Remove reference to Cosmetics. Update regulation reference.	CC-22-0338	S. Millar